EXHIBIT 1
McGilvery et al., Biochemistry: A Fundamental Approach 632-635 (2d ed. 1979)

SECOND EDITION

BIOCHEMISTRY

A Functional Approach

R. W. McGILVERY, Ph.D.

Professor of Biochemistry,
University of Virginia School of Medicine

in collaboration with

GERALD GOLDSTEIN, M.D.

Professor of Internal Medicine,
University of Virginia School of Medicine

1979

W. B. SAUNDERS COMPANY

Philadelphia / London / Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

Biochemistry – A Functional Approach

ISBN 0-7216-5912-8

Library of Congress catalog card number 79-4729.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

	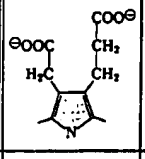	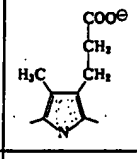	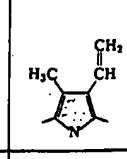	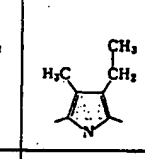	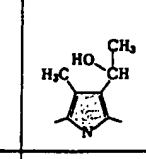	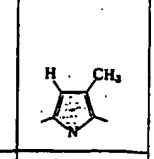
uroporphyrin	4	—	—	—	—	—
coproporphyrin	—	4	—	—	—	—
protoporphyrin	—	2	2	—	—	—
etioporphyrin	—	—	—	4	—	—
hematoporphyrin	—	2	—	—	2	—
mesoporphyrin	—	2	—	2	—	—
deuteroporphyrin	—	2	—	—	—	2

FIGURE 33–1 Kinds of porphyrins. The nature of the constituent pyrroles as listed at the top defines the porphyrin, and the number of the various pyrroles in different kinds of porphyrins is given. It is not hard to visualize sequences of decarboxylations, oxidations, hydrations, and reductions by which all of these could be formed from the parent uroporphyrins listed first.

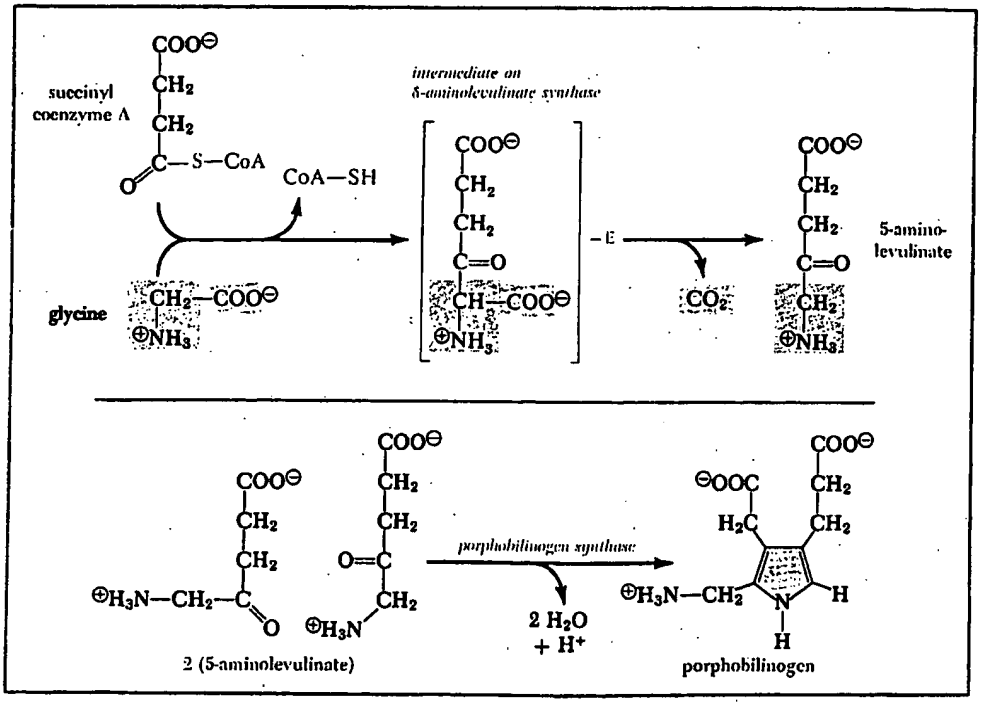

FIGURE 33–2 Porphyrin synthesis begins with two successive condensations by which a pyrrole ring is generated from two molecules each of succinyl coenzyme A and glycine.

Each of these four uroporphyrins is designated by a Roman numeral. (There are only four uroporphyrins because any other reversal of pyrrole groups beyond those shown is superimposable on one of the four by turning the ring over.)

Now, if two of the groups in uroporphyrin are changed into a third kind of group, which is the circumstance seen in protoporphyrins, then there are 15 possible combinations. Hans Fischer* wrote down the 15 possibilities, and showed that the porphyrin in hemoglobin had the same arrangement as the ninth he had tabulated. Hence, the porphyrin in heme is designated as protoporphyrin IX.

All natural porphyrins are derived from uroporphyrin I, in which there is a regular alternating sequence of groups, as might be expected if the pyrroles are combined head-to-tail, and from uroporphyrin III, which represents a reversal — an isomerization — of one of the pyrrole groups.

PORPHYRIN SYNTHESIS

The complex porphyrin molecule is made from two simple precursors, **succinyl coenzyme A** and **glycine** (Fig. 33–2). The initial reaction is a condensation of these compounds within mitochondria, where they are readily available, to form **5-aminolevulinate.** This is the rate-controlling step in porphyrin biosynthesis. The 5-aminolevulinate passes into the cytosol for the next step.

The reaction involves an intermediate condensation of glycine with pyridoxal phosphate. The mechanism is not shown; one of the H atoms on C-2 of glycine leaves after condensation; the resultant carbanion then unites with the electropositive carbonyl carbon of succinyl coenzyme A.

Two molecules of 5-aminolevulinate condense to form **porphobilinogen.** This is the parent pyrrole compound, and four molecules of it are combined to make **uroporphyrinogen III** (Fig. 33–3).

*Hans Fischer (1881–1945): German biochemist and Nobel Laureate. Not to be confused with Emil Fischer (1852–1919), also a German biochemist and Nobel Laureate, discoverer of much of the fundamental knowledge of the chemistry of proteins, carbohydrates, and nucleic acids; nor with Emil Fischer's late son, H. O. L. Fischer, a carbohydrate chemist of distinction at Toronto and Berkeley; nor with E. H. Fischer, very much alive at Seattle, and not bad as a biochemist, either. (This list is by no means exhaustive.)

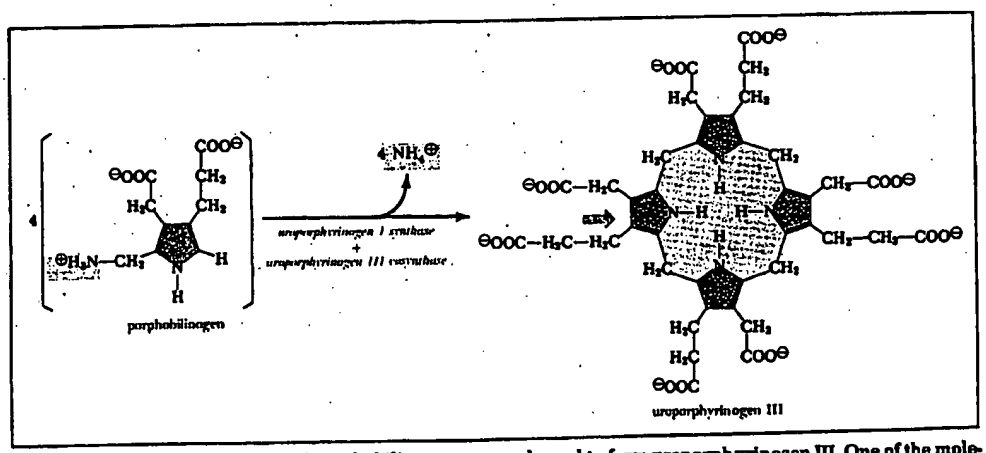

FIGURE 33–3 Four molecules of porphobilinogen are condensed to form uroporphyrinogen III. One of the molecules *(arrow)* condenses head-to-head in the presence of a cosynthase; the others condense head-to-tail.

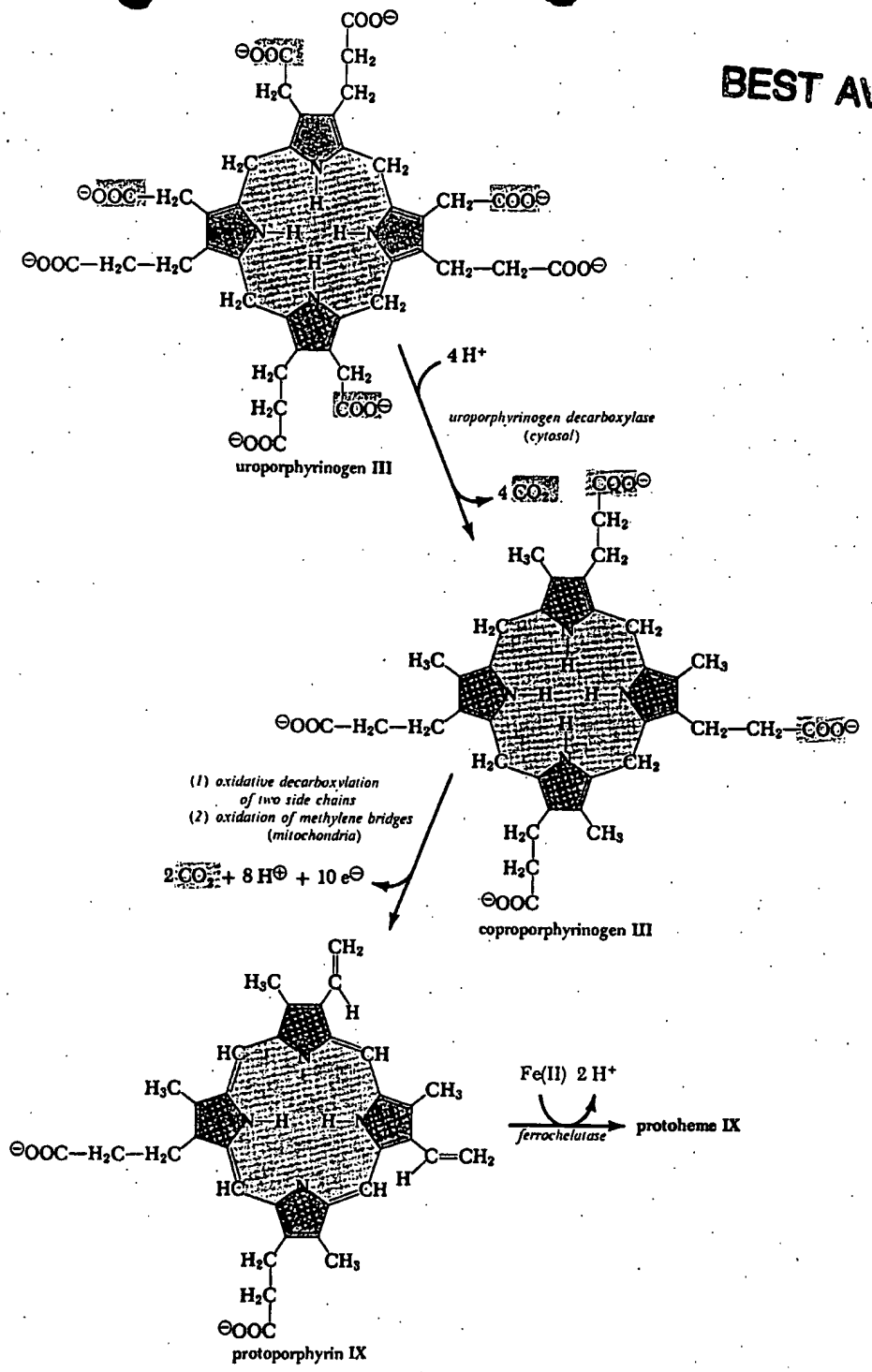

FIGURE 33-4 The conversion of uroporphyrinogen III to protoporphyrin IX and then to protoheme IX.

(The **porphyrinogens** are porphyrins in which the bridge atoms between pyrrole rings are in the reduced, or methylene, state, whereas these atoms are in the methylidyne state in porphyrins.) Two proteins are involved in this condensation. Uroporphyrinogen I synthase by itself would catalyze a simple head-to-tail condensation of porphobilinogen units, forming uroporphyrinogen I. The second protein, a uroporphyrinogen III cosynthase, has no apparent catalytic activity, but it somehow combines with the synthase so as to alter its specificity, causing one of the porphobilinogen molecules to condense head-to-head, creating a type III porphyrin. The mechanism is unknown.

The remaining steps (Figs. 33–4) involve decarboxylation of the aceto side chains to form methyl groups (coproporphyrinogen III), oxidative decarboxylation of two of the propiono side chains to form vinyl groups (protoporphyrinogen IX), and the oxidation of the methylene bridges to methylidyne bridges (protoporphyrin IX). The latter two steps are catalyzed by mitochondria, but it is not known where the enzymes are localized within the organelle. However, the final step of

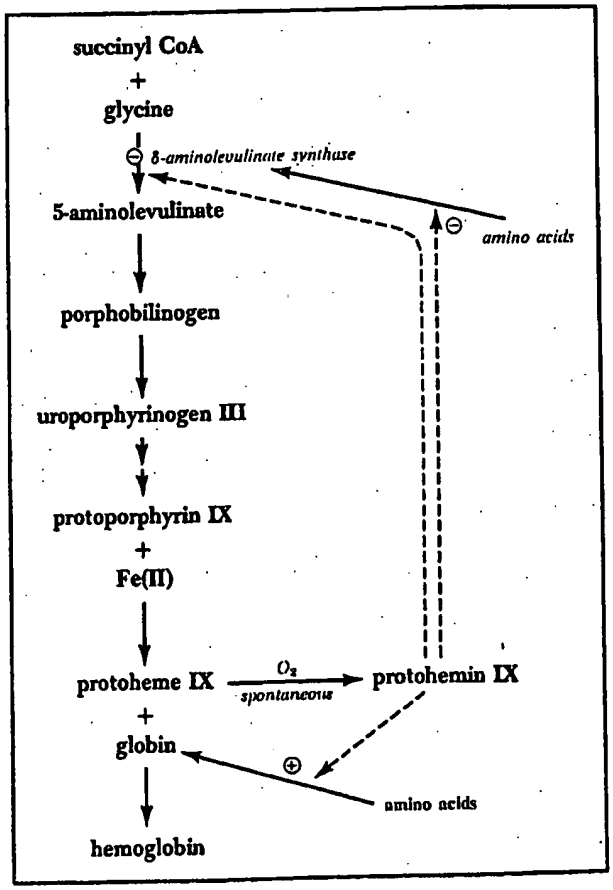

FIGURE 33–5

Regulation of hemoglobin synthesis by protohemin IX. Hemin forms when the supply of heme exceeds the supply of globin. The hemin suppresses formation of additional protoporphyrin, probably by direct inhibition of aminolevulinate synthase and also by repression of the enzyme's synthesis. The hemin also promotes synthesis of globin polypeptides.